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(71) Applicant *(for all designated States except US)*: BOEHRINGER MANNHEIM GMBH [DE/DE]; D-68298 Mannheim (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: OCHLICH, Peter-Paul [DE/DE]; Wallonenstrasse 34, D-69250 Schönau (DE). MÜLLER-BECKMANN, Bernd [DE/DE]; Auf dem Leimen 19, D-67269 Grünstadt (DE).

(74) Agents: MINK, Reinhold et al.; Boehringer Mannheim GmbH, Patentabteilung, D-68298 Mannheim (DE).

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(54) Title: PHARMACEUTICAL ADMINISTRATION FORM OF PARATHYROID HORMONE HAVING AN ACTIVE INGREDIENT RELEASE PERIOD OF FROM TWO TO SIX HOURS

(57) Abstract

The present invention is directed to a pharmaceutical administration form of parathyroid hormone or parathyroid hormone derivatives having an active ingredient release period of from two to six hours, the use of parathyroid hormone for the preparation of such pharmaceutical administration forms, and to a method for treating osteoporosis in the human body.

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Pharmaceutical Administration Form of Parathyroid Hormone Having an Active Ingredient Release Period of from Two to Six Hours

The present invention is directed to a pharmaceutical administration form of parathyroid hormone or parathyroid hormone derivatives having an active ingredient release period of from two to six hours, the use of parathyroid hormone in the treatment of osteoporosis by applying said pharmaceutical administration form, and a method for the treatment of osteoporosis in the human body.

Parathyroid hormone and N-terminal parathyroid hormone fragments are known to have osteogenous activity which has been observed in animal experimental studies on rats as well as in clinical studies on osteoporotic patients and has been described in technical literature (Selye, Endocrinology 16 (1932), 547-558; Hefti et al., Clin. Sci. 62 (1982), 389-396; Gunnes-Hey et al., Metab. Bone Dis. Relat. Res. 5 (1984), 177-181; Reeve et al., Br. Med. J. 280 (1980), 1340-1344; Slovik et al., J. Bone Miner. Res. 1 (1986), 377-381, EP 0,197,514).

There is general agreement in the art about the fact that the osteogenous activity of PTH is bound to a pulsatile or intermittent application. Pulsatile application of PTH in animal experimental as well as in clinical studies on patients resulted in an increase of bone matter (Tam et al., Endocrinology 110(2) (1982), 506-512; Podbesek et al., Endocrinology 112(3) (1983), 1000-1006; Hock et al., J. Bone Miner. Res. 7(1) (1992), 65-72; Reeve et al., Br. Med. J. 280 (1980), 1340-1344; Slovik et al., J. Bone Miner. Res. 1 (1986), 377-381).

While in animal experiments an increased bone transformation rate was observed with continuous infusion of PTH, this, however, did not result in a net gain of bone matter (Tam et al., Endocrinology 110 (2) (1982), 506-512; Malluche et al., Am. J. Physiol.

242(2) (1982), F197-F201; Hock et al., J. Bone Miner. Res. 7(1) (1992), 65-72; Podbesek et al., Endocrinology 112(3) (1983), 1000-1006).

Surprisingly, it has now been found that continuous application of PTH or derivatives thereof certainly results in a net gain of bone matter, when limited to up to six hours.

Therefore, the invention is directed to a pharmaceutical administration form of PTH or derivatives thereof having an active ingredient release period of from two to six hours, and preferably of four hours. Here, the pharmaceutical administration form may be an infusion solution or a transdermic or enteric pharmaceutical system having an active ingredient release period of up to six hours. Compared to pulsatile application which in all hitherto known animal experimental and clinical studies has been effected as a daily subcutaneous injection, the transdermic or enteric application of PTH offers the decisive advantage of retarded active ingredient release. Abrupt PTH pulses and the associated substantial disturbance of the patient's well-being due to the necessary injection can be dismissed.

According to the present invention, the pharmaceutical administration form contains biologically active parathyroid hormone or parathyroid hormone derivatives, particularly human PTH(1-84) or an N-terminal human PTH fragment having the sequences 1-29 to 1-41, preferably the sequences 1-34, 1-35, 1-36, 1-37, or 1-38. Furthermore, PTH-analogous peptides, variants or modifications of parathyroid hormone (PTH agonists) resulting from the replacement of single or multiple amino acids in the amino acid sequence of unmodified parathyroid hormone may also be employed. In addition, PTH fragments appropriately abridged at the N terminus and/or the C terminus are also possible within the meaning of the invention. Such fragments have been described in WO 90/10067, EP 0,301,484 or EP 0,301,485, for example.

Application of the PTH peptides is effected in such a manner that release of the pharmacologically active substance in the body within a period of from 2 to 6 hours is ensured. Such release may be obtained in different ways. One method is to administer the

required amount of PTH intravenously over the appropriate period of time. Another method involves transdermic application, releasing the active ingredient within the desired period of time. This may be effected using a patch which is applied to the skin for the desired period of time. By adding permeation accelerators, release of the active ingredient through the skin as regularly as possible can be ensured so that during application of the patch to the skin, continuous release of the active ingredient and permeation through the skin take place. Another way of transdermic application involves iontophoresis. To this end, an appropriate dosage unit (iontophoretic patch) is applied to the skin, and release of the active ingredient through the skin within the desired period of time is controlled by applying an electrical potential.

Preferably, loaded liposomes, microspheres made of common polymers, or proteinoid complexes ensuring resorption of the active ingredient in the small intestine over an appropriate period of time are possible as enteric pharmaceutical systems.

According to the invention, PTH or a PTH fragment may be administered in the form of a continuous infusion preferably over two to six hours, particularly about four hours. Here, a tendency to higher anabolic activity can be observed following an infusion of about four hours compared to a one hour infusion or subcutaneous bolus administration. An exceedingly good osteogenous activity was observed following a four hour intravenous infusion of hPTH(1-34) on five working days within two successive weeks.

Further examinations using PTH(1-37) showed that levels maintained for 8 hours at 80 µg/kg iv, i.e., at the same infusion rate as 40 µg/kg iv over 4 hours, give rise to severe adverse effects on the bones, while at 40 µg/kg PTH(1-37) iv over 4 hours a distinct osteoanabolic effect occurs. In contrast, intravenous bolus injection of 80 µg/kg PTH(1-37) within about one minute does not result in negative but positive effects with respect to the relative X-ray density and the Ca content. However, the therapeutic utility of comparably high intravenous PTH doses in the form of a bolus administration is not deemed advantageous due to severe circulatory effects to be expected.

Preferably, water is used as injection medium, containing additives common with injection solutions, such as stabilizers, solubilizers and buffers. Such additives are, e.g., tartrate and citrate buffers, ethanol, complexing agents such as ethylenediaminetetra-acetic acid and non-toxic salts thereof, high molecular weight polymers such as liquid poly(ethylene oxide) for viscosity control. Liquid carrier substances must be sterile and are preferably filled into ampoules.

The dosage may depend on various factors such as mode of application, species, age or individual condition. Usually, from 30 to 50 µg/kg/day are administered.

In addition, the invention relates to the use of parathyroid hormone or a parathyroid hormone derivative in the treatment of osteoporosis by application in the form of a continuous infusion for two to six hours or a transdermic or enteric administration form having an active ingredient release period of from two to six hours. Such examinations relating to the use of PTH or PTH fragments, according to the invention, will be subject to protection, particularly within the scope of clinical tests for the purpose of authorization according to the drug law. As a rule, the corresponding petitioned authorization according to the drug law relates to the treatment of calcium-metabolic diseases in general and to the treatment of osteoporosis, in particular.

Likewise, the invention is directed to a method for osteoporosis treatment of the human body wherein, in order to increase the bone matter, a therapeutically effective amount of parathyroid hormone or parathyroid hormone derivative is applied in the form of a continuous infusion for two to six hours or a transdermic or enteric administration form having an active ingredient release period of from two to six hours. Preferably, the method according to the invention is conducted within the scope of clinical tests for the purpose of authorization according to the drug law.

In the following, the invention will be illustrated in more detail by way of embodiments.

Example 1

Infusion of PTH for various periods of time

In a pre-operation, a venous permanent catheter was implanted in male Wistar rats weighing about 230-250 g. The animals were assigned to 5 different groups of treatment of 6 animals each, which were treated as follows:

1. Rinsing the catheter with solvent on 5 working days within two successive weeks = negative control.

2. Intravenous infusion of hPTH(1-34), 40 µg/kg/day within one hour on 5 working days within two successive weeks.

3. Intravenous infusion of hPTH(1-34), 40 µg/kg/day within four hours on 5 working days within two successive weeks.

4. Intravenous infusion of hPTH(1-34), 40 µg/kg/day within eight hours on 5 working days within two successive weeks.

5. Subcutaneous bolus injection of hPTH(1-34), 40 µg/kg/day on 5 working days within two successive weeks = positive control.

6. In another experiment, PTH(1-37) was tested under various conditions. The comparison comprises intravenous infusion of 40 µg/kg and 80 µg/kg over four and eight hours, respectively, as well as subcutaneous injection of 40 µg/kg and intravenous bolus injection of 80 µg/kg.

On the third day following the last treatment, the animals were sacrificed and the femora were removed for subsequent analysis of femur weight, volume, dry weight, ash weight, and calcium content.

The results for PTH(1-34) are summarized in the following Table 1. showing that a significant increase of bone matter was observed in the Treatment Groups 1 (1 hour infusion), 2 (4 hours infusion) and 4 (sc bolus), while no differences compared to the control group occurred in Group 3 (8 hours infusion).

Table 1

Continuous infusion of PTH(1-34) on rats (Wistar)

Duration of treatment:

Continuous infusion for 1 hour (Group 1), 4 hours (Group 2), 8 hours (Group 3) once per day iv, and once per day subcutaneous (sc) (Group 4).

Dose: 40 µg PTH(1-34)/kg/day

n = 5 - 6

Duration of infusion	**Control**	**Group 1 1 hour iv**	**Group 2 4 hours iv**	**Group 3 8 hours iv**	**Group 4 sc**
Length (mm)					
Median	34	34	34	34	34
1st quart.	34	34	34	33	34
3rd quart.	34	35	34	34	34
Volume (µl)					
Median	645	648	672	680	639
1st quart.	628	639	645	642	627
3rd quart.	675	670	679	683	668
Dry weight (mg)					
Median	458	499	520	471	512
1st quart.	445	479	518	458	493
3rd quart.	473	517	539	503	522
Ash weight (mg)					
Median	278	308	328	280	316
1st quart.	270	296	323	278	306
3rd quart.	288	320	337	308	321

Duration of infusion	Control	Group 1 1 hour iv	Group 2 4 hours iv	Group 3 8 hours iv	Group 4 sc
Ca content (mg)					
Median	100	113	123	102	115
1st quart.	98	109	115	99	115
3rd quart.	106	116	131	112	116
Dry Weight/Volume (mg/ml)					
Median	707	758	794	710	786
1st quart.	682	747	773	671	776
3rd quart.	715	784	820	740	795
Ash Weight/Volume (mg/ml)					
Median	428	468	497	433	488
1st quart.	412	459	481	401	479
3rd quart.	438	485	519	453	490
Ca Content/Volume (mg/ml)					
Median	155	171	192	155	175
1st quart.	152	170	171	145	171
3rd quart.	158	176	193	164	180

In one test series of PTH(1-37) the influence of duration at an identical infusion rate (40 µg/kg iv over four hours; 80 µg/kg iv over eight hours) was examined. Here, it appeared that a significant osteoanabolic effect occurred at 40 µg/kg PTH(1-37) iv over four hours, while the double infusion time period of eight hours at an overall amount of 80 µg/kg iv resulted in dramatic negative effects on the bone balance. In contrast, repeated intravenous bolus injection of 80 µg/kg within about one minute had a positive effect on the bone balance. However, the therapeutic utility of comparably high intravenous PTH doses in the form of a bolus administration is not deemed advantageous due to the relatively small effect and, in particular, due to severe circulatory effects to be expected.

The results for PTH(1-37) are summarized in Table 2.

Table 2

a) Effect of PTH(1-37) by intravenous infusion on rats

Duration of treatment: 10 working days, once per day

Dose: 40 (4 hours) and 80 (8 hours) µg/kg/day, respectively

Infusion rate: 10 µg/kg/hour

Group 1: 4 hours iv; 40 µg/kg/day

Group 2: 8 hours iv; 80 µg/kg/day

Group 3: subcutaneous (sc); 40 µg/kg/day

n = 7 - 10

Duration of infusion	**Control**	**Group 1 4 hours iv**	**Group 2 8 hours iv**	**Group 3 sc**
Relative X-Ray Density (mmAl)				
Median	1.5	2.0	1.5	1.8
1st quart.	1.3	2.0	1.3	1.7
3rd quart.	1.6	2.2	1.7	1.8
Length (mm)				
Median	36	35	34	36
1st quart.	35	35	34	36
3rd quart.	36	36	35	36
Volume (µl)				
Median	709	786	737	775
1st quart.	659	752	692	710
3rd quart.	735	803	831	814

Duration of infusion	Control	Group 1 4 hours iv	Group 2 8 hours iv	Group 3 sc
Dry Weight (mg)				
Median	515	600	424	599
1st quart.	476	581	420	570
3rd quart.	535	608	500	633
Ash Weight (mg)				
Median	329	381	262	384
1st quart.	308	377	256	357
3rd quart.	336	388	330	398
Ca Content (mg)				
Median	119	138	95	140
1st quart.	111	137	93	132
3rd quart.	120	140	119	145
Dry Weight/Volume (mg/ml)				
Median	716	770	593	768
1st quart.	709	756	533	743
3rd quart.	736	785	618	779
Ash Weight/Volume (mg/ml)				
Median	460	490	356	484
1st quart.	450	480	319	467
3rd quart.	474	506	384	487
Ca Content/Volume (mg/ml)				
Median	167	177	134	177
1st quart.	164	174	116	170
3rd quart.	172	181	158	179

b) Effect of PTH(1-37) by intravenous bolus administration on rats

Duration of treatment: 10 working days, once per day

Dose: 80 µg/kg/day

Infusion rate: 10 µg/kg/hour

Group 4: intravenous bolus administration

n = 7 - 10

	Control	**Group 4 Bolus iv**
Relative X-Ray Density (mmAl)		
Median	1.0	1.3
1st quart.	0.9	1.2
3rd quart.	1.0	1.3
Length (mm)		
Median	35	35
1st quart.	35	34
3rd quart.	35	36
Volume (µl)		
Median	562	635
1st quart.	522	624
3rd quart.	641	714
Dry Weight (mg)		
Median	449	517
1st quart.	426	487
3rd quart.	466	548
Ash Weight (mg)		
Median	299	348
1st quart.	293	329
3rd quart.	313	366
Ca Content (mg)		
Median	102	119
1st quart.	101	114
3rd quart.	106	126

	Control	Group 4 Bolus iv
Dry Weight/Volume (mg/ml)		
Median	771	800
1st quart.	726	754
3rd quart.	817	829
Ash Weight/Volume (mg/ml)		
Median	513	527
1st quart.	483	507
3rd quart.	561	549
Ca Content/Volume (mg/ml)		
Median	175	182
1st quart.	165	176
3rd quart.	191	189

Example 2

Iontophoretic application of PTH

A pilot experiment on transdermic application by iontophoresis was conducted on two rabbits. The animals were trimmed in the flanks, and the skin was cleaned with ethanol. A filter paper soaked with hPTH(1-34) solution was placed on the skin and fixated with a chlorinated silver electrode. Iontophoresis was carried out over a time period of 90 and 105 minutes, respectively, under the following conditions: current intensity: 5-7 mA, current density: 0.44-0.62 mA/cm^2, current pulses: 8 ms at 2 ms intervals. During the experiment, blood was taken from the ear artery at various times (see table below), and the serum obtained was deep frozen. Using the Nichols RIA INS-PTH, the PTH concentration in the serum samples was measured.

Result: In both animals. a significant level of hPTH(1-34) could be detected after a period of 1 to 1.5 hours.

hPTH(1-34) [pg/ml]

	Time [min]							
	0	20	30	45	60	90	105	120
Animal 1	36	112			123	1834		
Animal 2	52		107	112	391	915	1420	1315

CLAIMS:

1. A pharmaceutical administration form, containing parathyroid hormone (PTH) or a parathyroid hormone derivative as the active ingredient, with an active ingredient release period of from two to six hours.

2. The administration form according to claim 1, comprising an infusion solution for continuous infusion of from two to six hours and preferably, four hours.

3. The administration form according to claim 1, comprising a transdermic pharmaceutical system, preferably a patch or an iontophoretic system.

4. The administration form according to claim 1, comprising an enteric pharmaceutical system, preferably loaded liposomes, or microspheres made of common polymers, or proteinoid complexes.

5. The administration form according to one of claims 1 to 4, containing human PTH(1-84).

6. The administration form according to one of claims 1 to 4, containing the N-terminal fragments of human PTH comprising the sequences 1-29 through 1-41, preferably 1-34, 1-35, 1-36, 1-37, and 1-38.

7. Use of parathyroid hormone or parathyroid hormone derivatives for the preparation of an administration form having an active ingredient release period of from two to six hours.

8. The use according to claim 7 for the preparation of an infusion solution for continuous infusion of from two to six hours and preferably, four hours.

9. The use according to claim 7 for the preparation of a transdermic or enteric administration form.

10. A method for osteoporosis treatment of the human body wherein, in order to increase the bone matter, a therapeutically effective amount of parathyroid hormone or parathyroid hormone derivative is applied in the form of a continuous infusion for two to six hours or a transdermic or enteric administration form having an active ingredient release period of from two to six hours.

11. The method according to claim 10, conducted within the scope of clinical tests for the purpose of authorization according to the drug law.

12. The method according to claim 10 or 11, wherein from 30 to 50 µg/kg/day parathyroid hormone or parathyroid hormone derivative is used as therapeutically effective amount.

13. The method according to one of claims 10 to 12, wherein said continuous infusion is effected on 5 working days within two successive weeks.

14. The method according to one of claims 10 to 12, wherein said transdermic application is effected using a patch optionally containing permeation accelerators, or by iontophoresis.

15. The method according to one of claims 10 to 12, wherein said enteric application is effected using loaded liposomes, microspheres made of common polymers, or proteinoid complexes.

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/EP 96/01962

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/29 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 643 981 (TAKEDA CHEMICAL INDUSTRIES) 22 March 1995 see claims 1,16,24,25 see page 6, line 47 - line 55	1,3,5-7, 9-12,14
X	WO,A,87 00750 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 12 February 1987 see claims 10-12 see page 6, line 33 - page 7, line 18 see page 9, line 1 - line 10; table 2	1,4-7, 9-12,15
A	WO,A,91 06564 (FORSSMAN, WOLF-GEORG) 16 May 1991 see claims 1,5,15	1,2,7,8, 10-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
3 September 1996	16. 09. 96

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

rnational application No.

PCT/EP 96/ 01962

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 10-15 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

nformation on patent family members

Inter ''onal Application No
PC1/EP 96/01962

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